

Neurologic Complications of Diabetes

- Define complications
- Glucose mediated oxidative stress produces complications
- Peripheral neuropathy
- EDIC results: ? Metabolic memory
- Cardiac autonomic neuropathy
- Surrogate markers: sera, urine, skin biopsies
- New NIH initiative: AMDCC

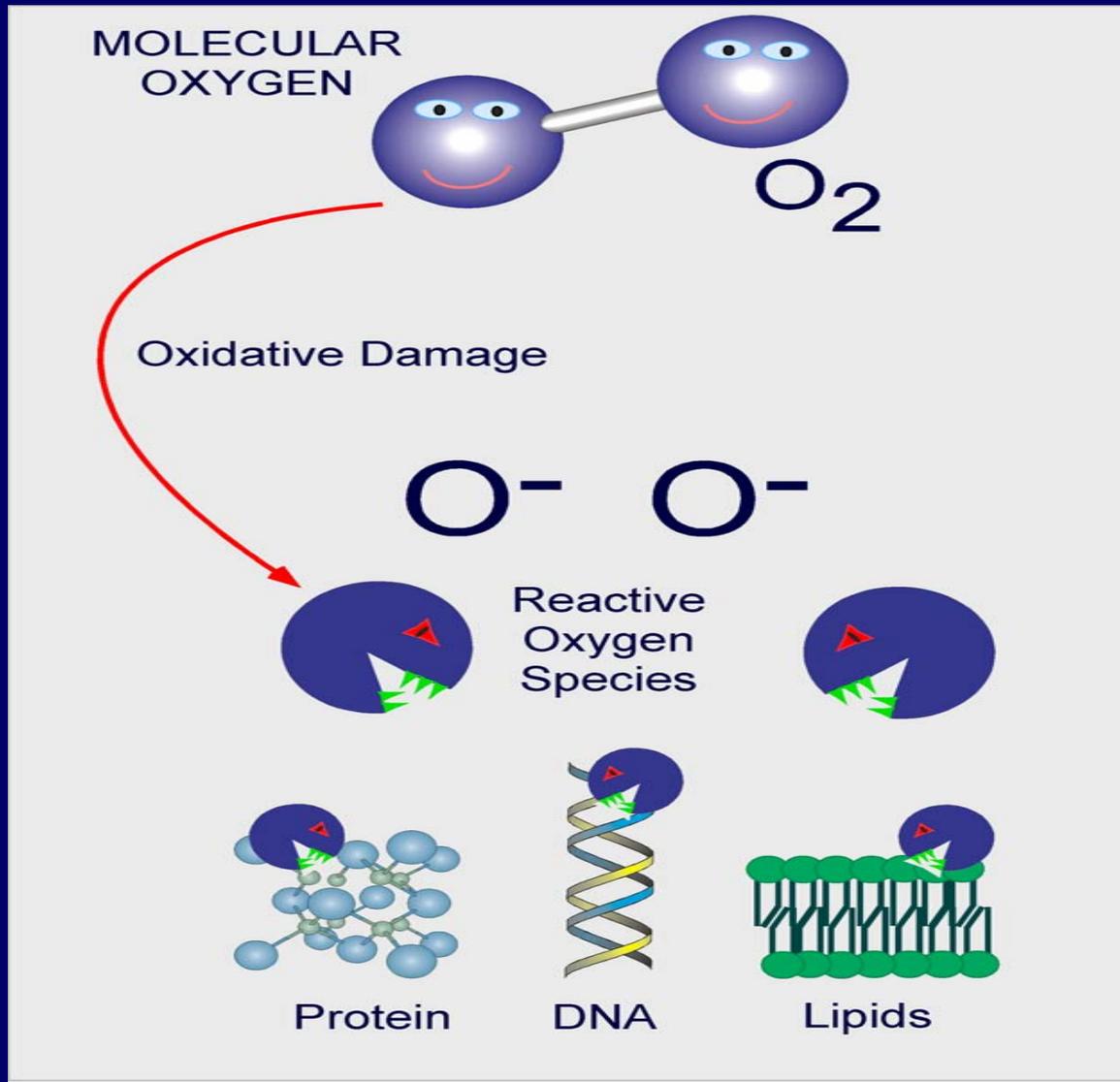
Neurologic Complications of Diabetes

- Macrovascular
 - Large vessel disease: stroke, large vessel ischemia
- Microvascular
 - Peripheral Neuropathy
 - Autonomic Neuropathy
 - These complications also occur in patients with IGT (Pre-diabetes)
 - Unique to diabetes

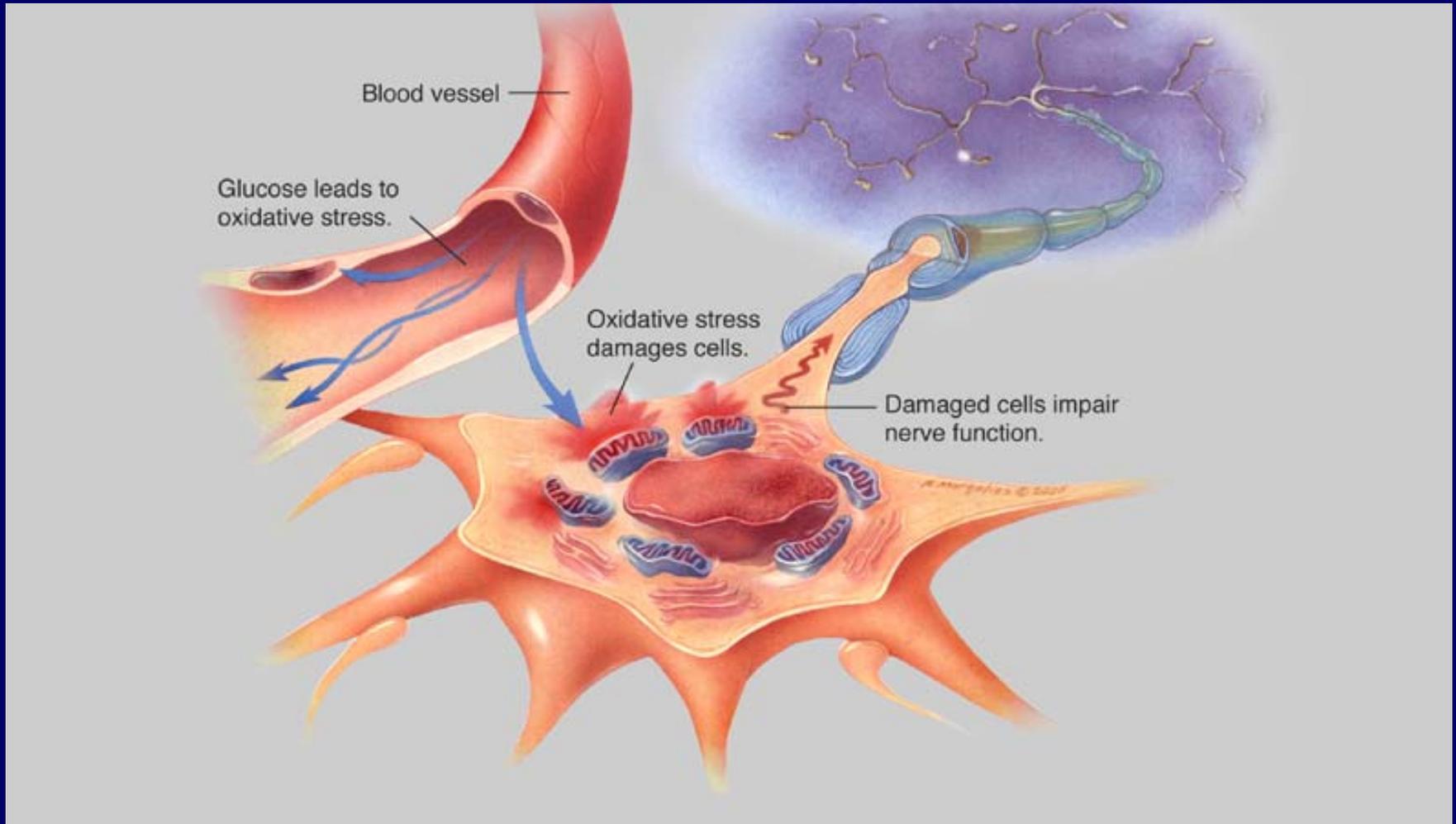
Why Are the Peripheral and Autonomic Nervous Systems Damaged in Diabetes?

- High glucose results in oxidative stress
- Oxidative Stress: energy depletion and free radicals
- Oxidative stress results in the break down of energy stores, genetic material, proteins and lipids
- End Result: Cellular dysfunction that underlies neurologic diabetic complications

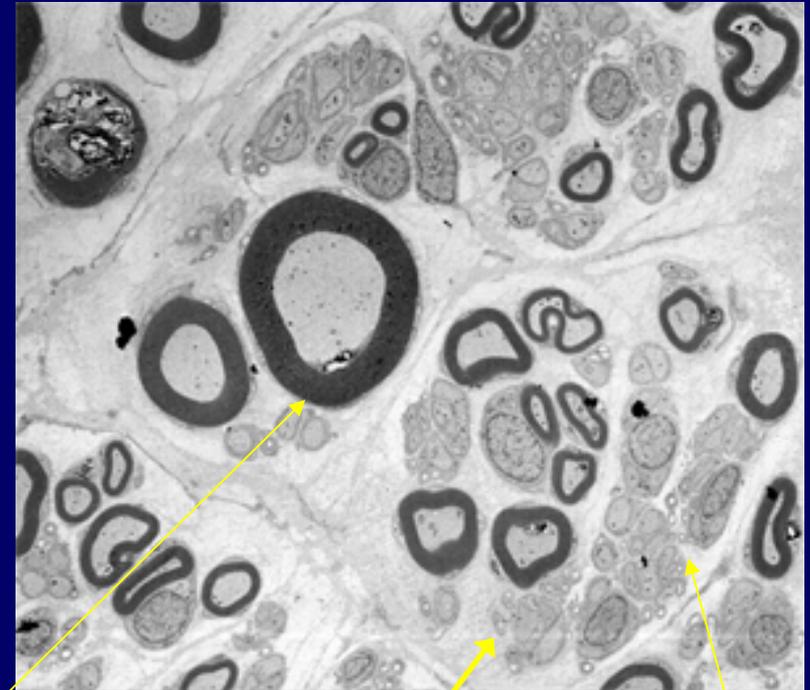
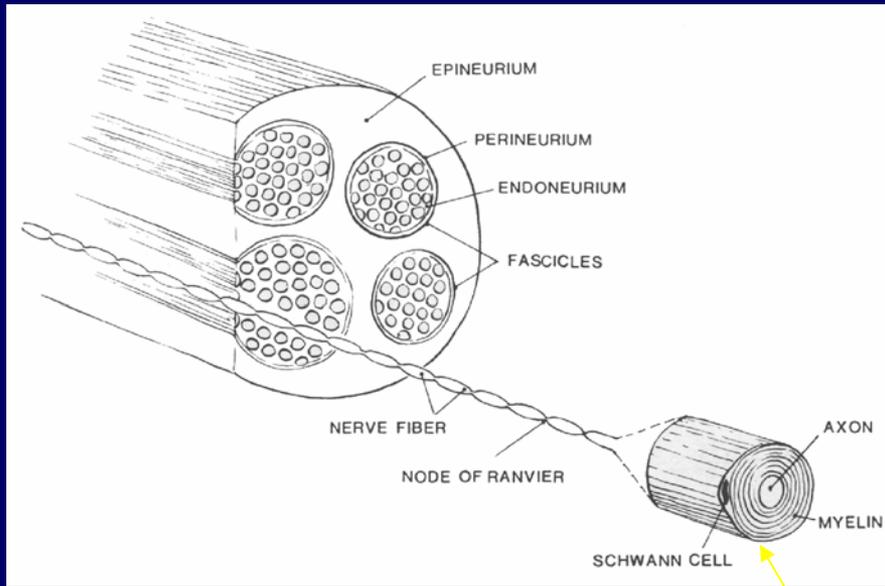
Reactive Oxygen Species (ROS) Mediate Cellular Damage and Death



Diabetic Peripheral and Autonomic Neuropathy



Nerve Fiber Types



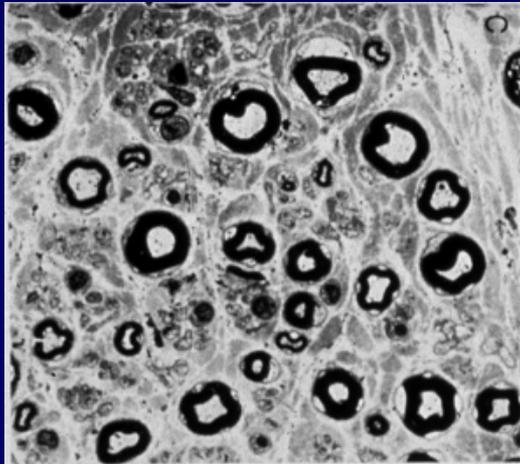
Large myelinated
fibers

Small myelinated
fiber

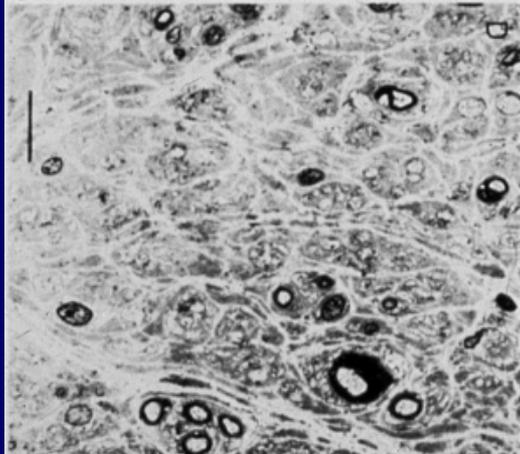
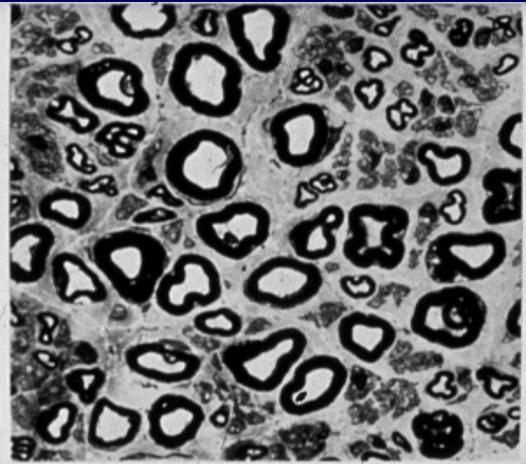
Unmyelinated
fibers

Progressive Axonal Loss in Diabetic Neuropathy

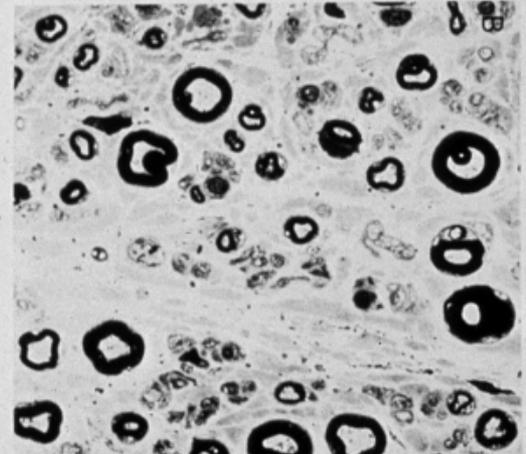
Mild



Normal

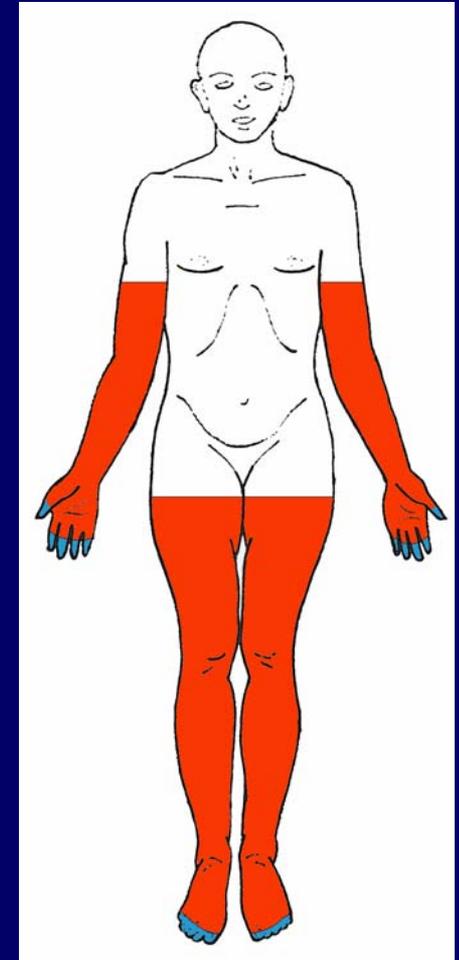
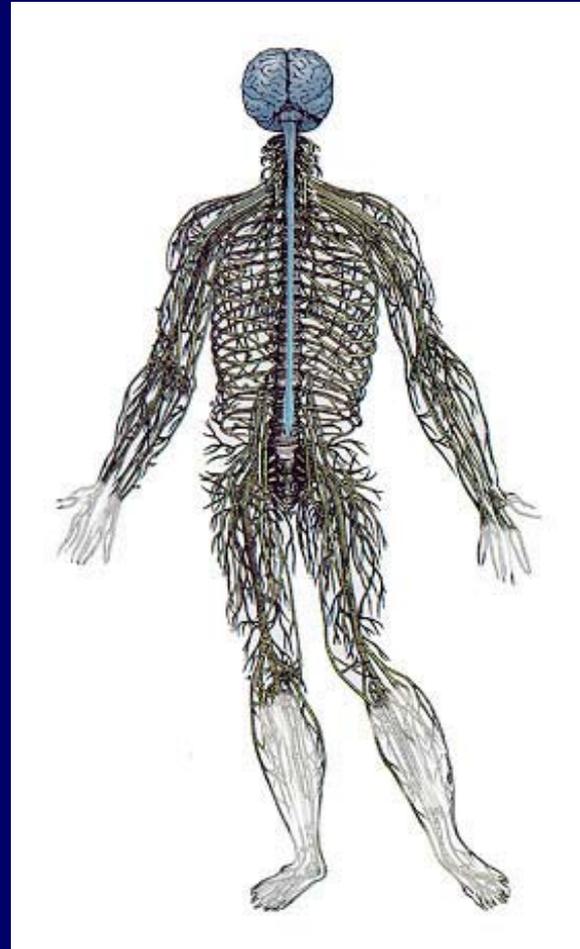
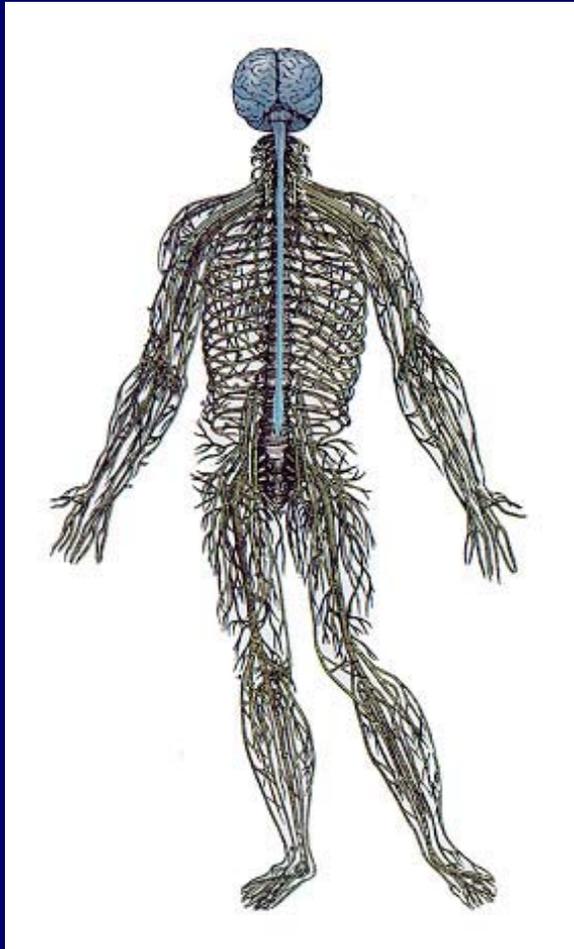


Severe

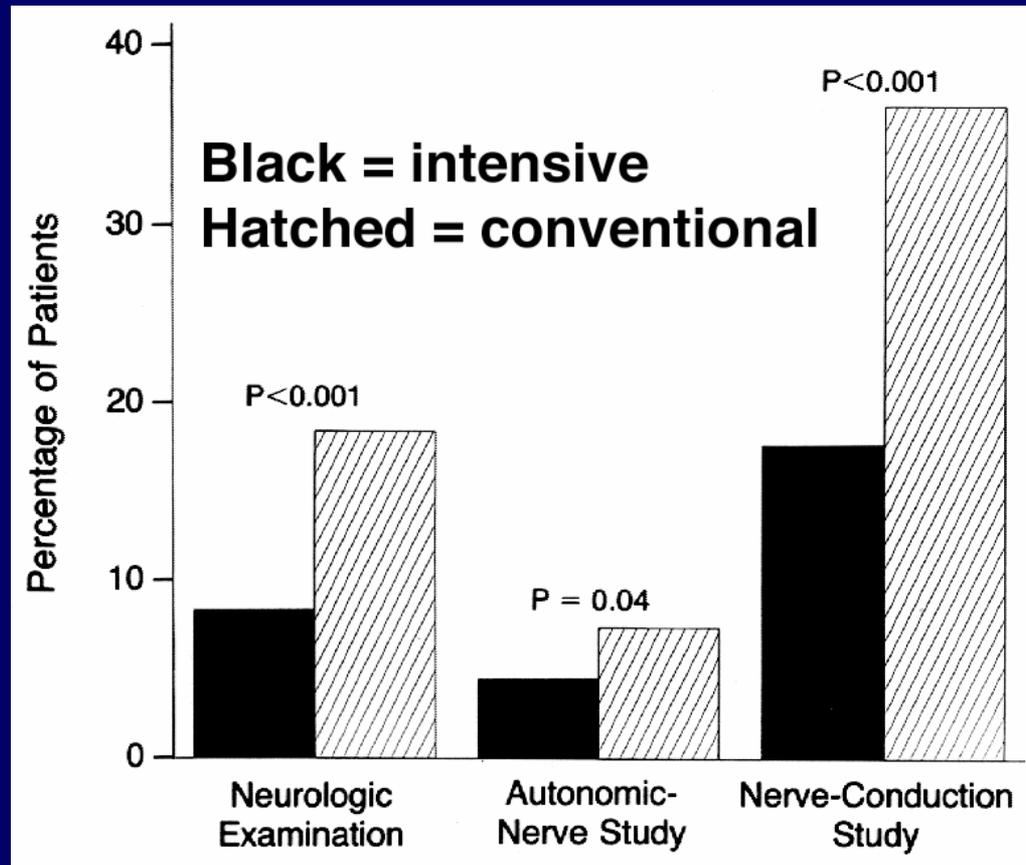


Moderate

Peripheral Neuropathy



DCCT Neurological Outcome

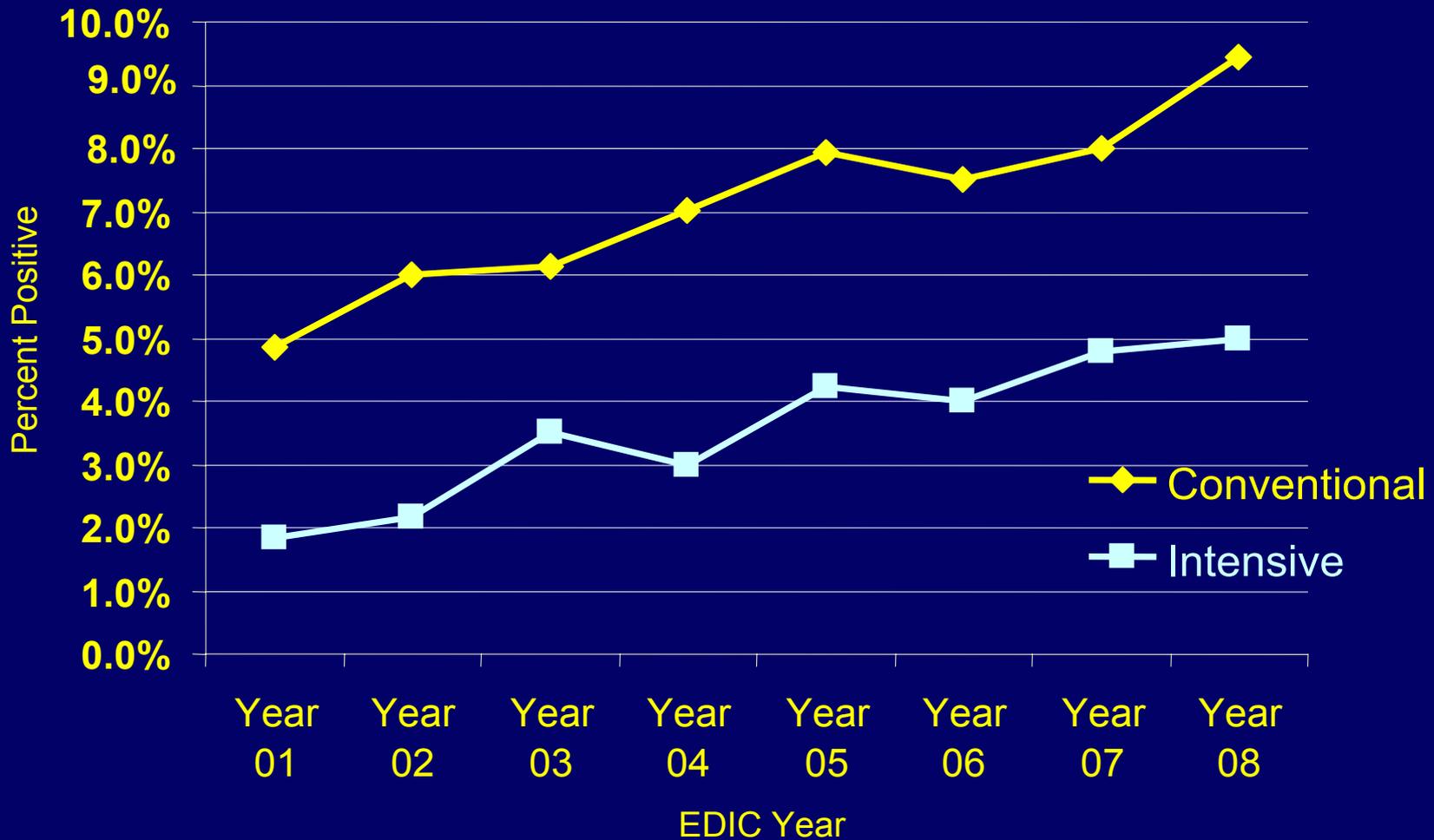


Adapted from DCCT Research Group. New Engl J Med 1993; 329:977-986

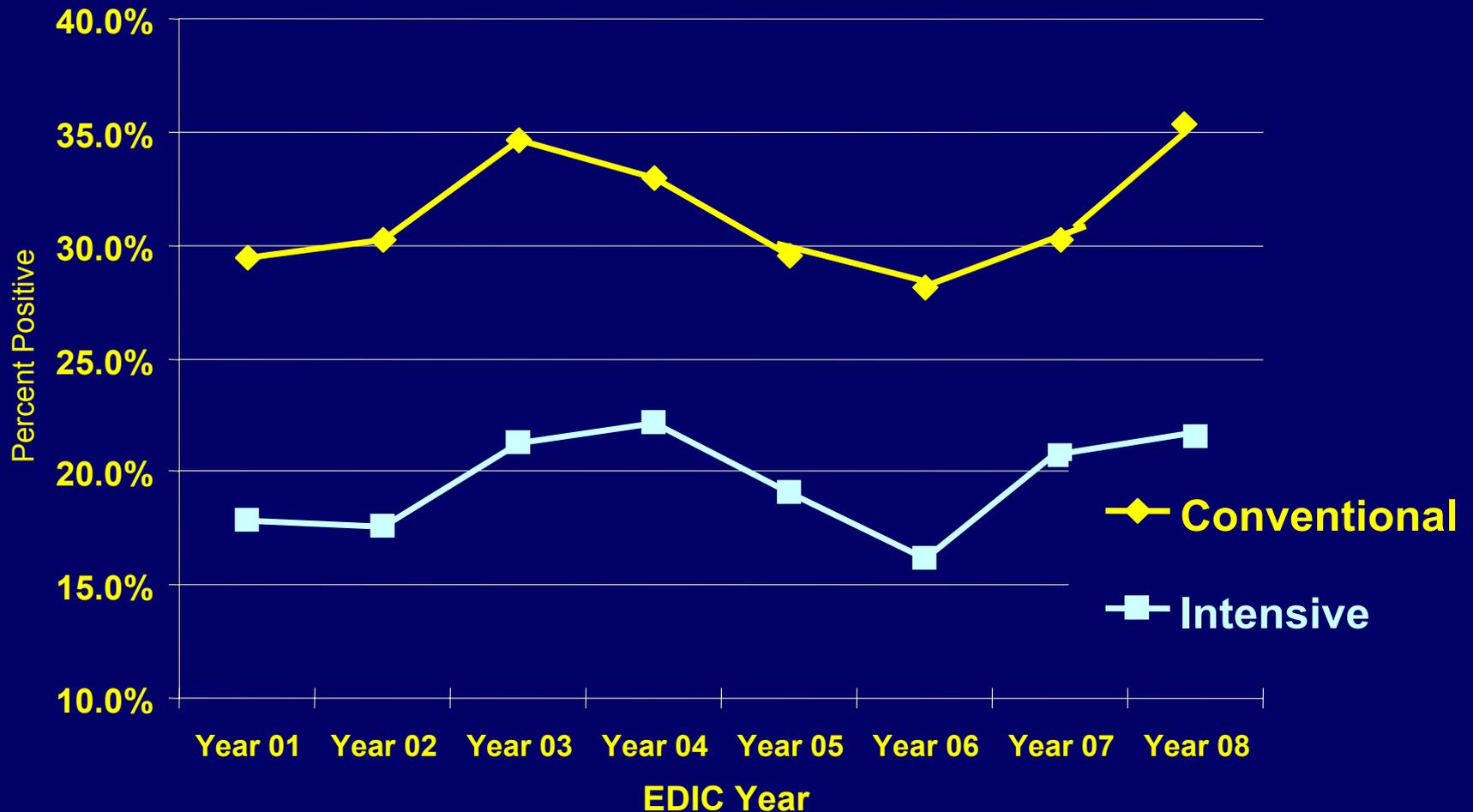
EDIC Design: MNSI

- DPN: Clinical symptoms and exam
- Completed by study coordinators
- Symptoms: simple questions
- Clinical exam [inspection, sensation (vibration, monofilament), reflexes]
- efeldman@umich.edu

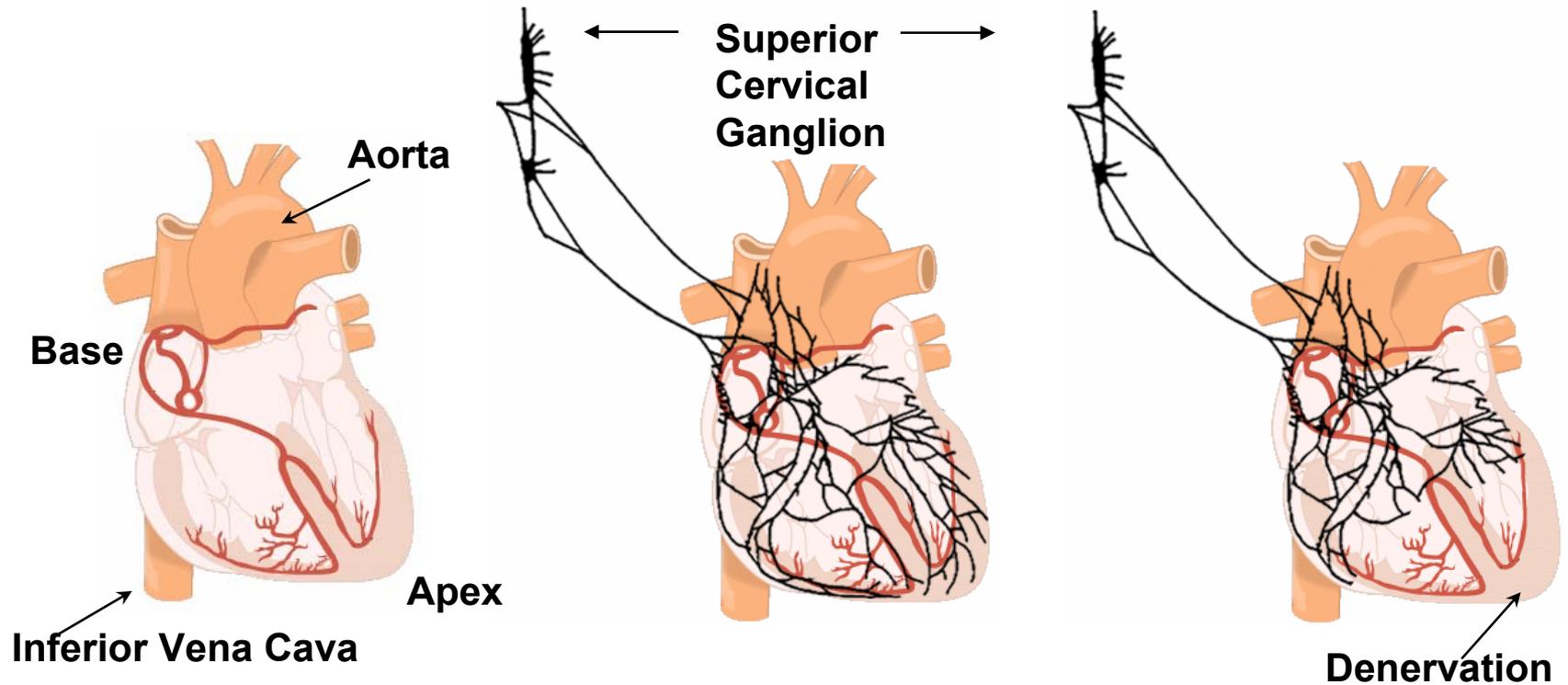
Neuropathy by Symptoms in EDIC Years 1-8



Neuropathy by Exam in EDIC Years 1-8



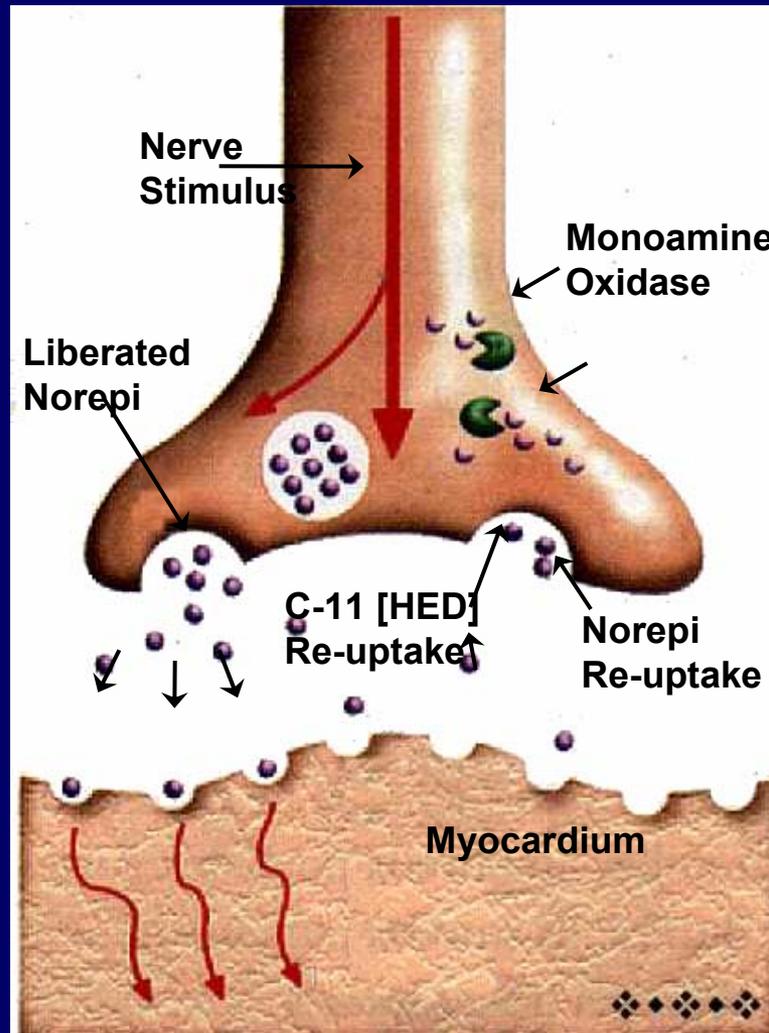
Cardiac Diabetic Autonomic Neuropathy



Positron Emission Tomography (PET) Scanning Measures Heart Function and Diabetic Autonomic Neuropathy

- PET scans visualize the blood flow to the heart using an ammonia (N-13) tracer
- PET scans visualize the sympathetic nerve innervation of the heart using hydroxyephedrine (C-11 HED) as a tracer
- Looking at both tracers together allows a comparison of heart blood flow with heart innervation

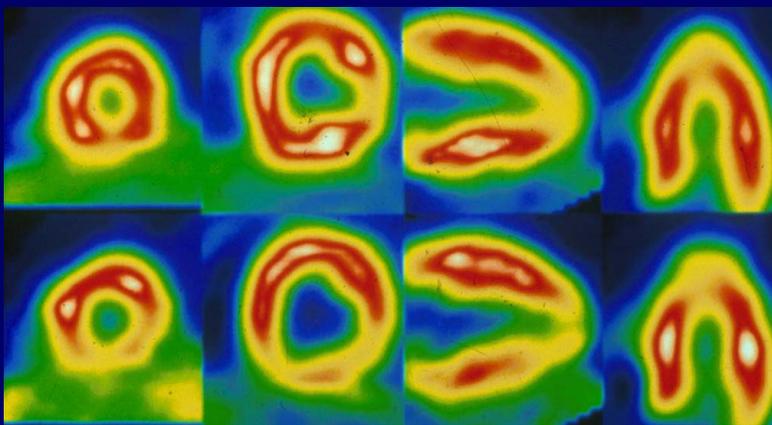
The Sympathetic Nerve Myocardial Synapse



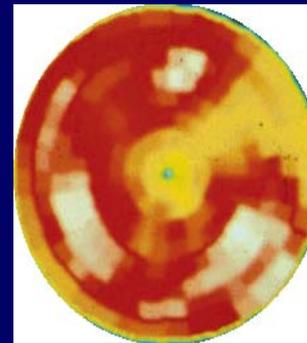
Early Cardiac Sympathetic Denervation in Diabetes

N-13 Ammonia Blood Flow

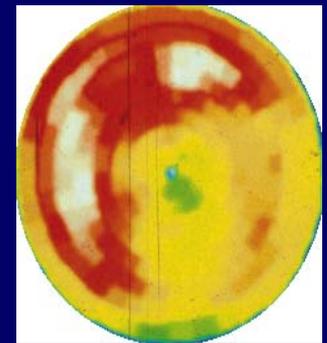
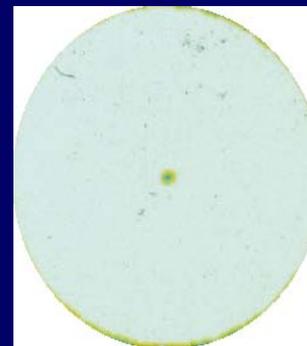
Distal Proximal Vertical Horizontal
Short Axis Short Axis Long Axis Long Axis



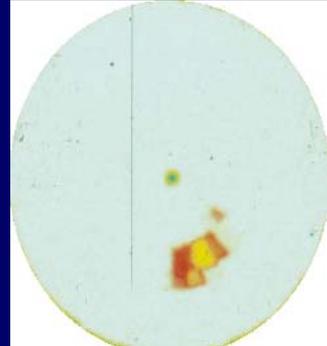
C-11 HED



FLOW



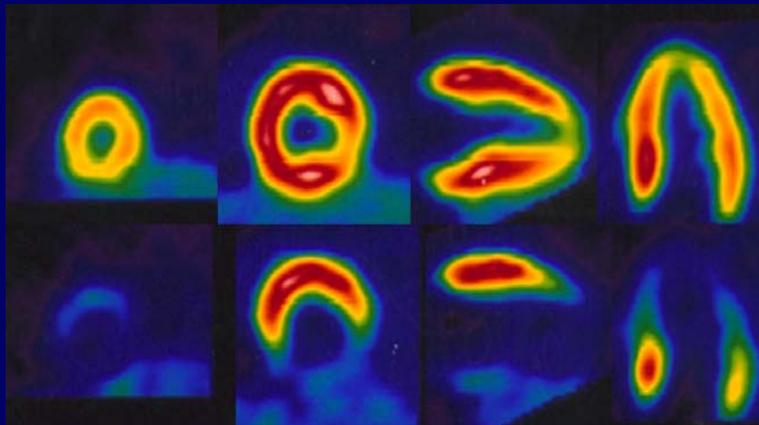
C-11 HED



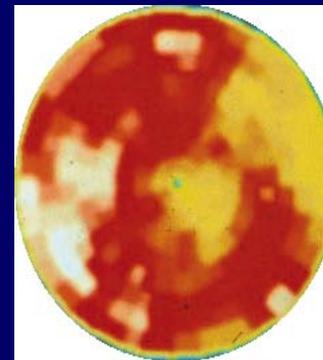
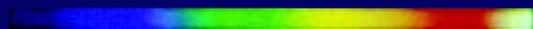
Advanced Cardiac Sympathetic Denervation in Diabetes

N-13 Ammonia Blood Flow

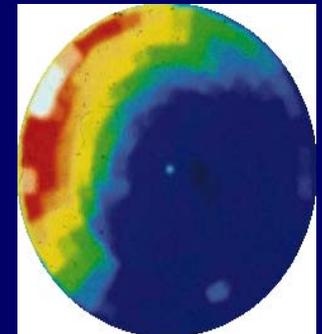
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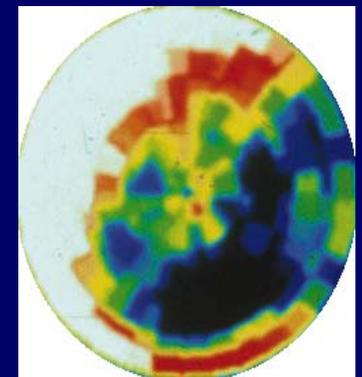
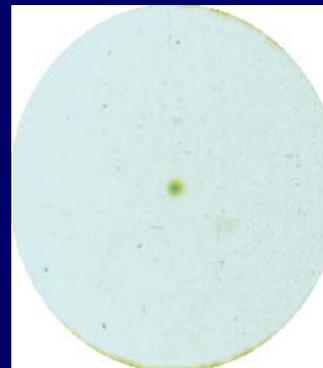
C-11 HED



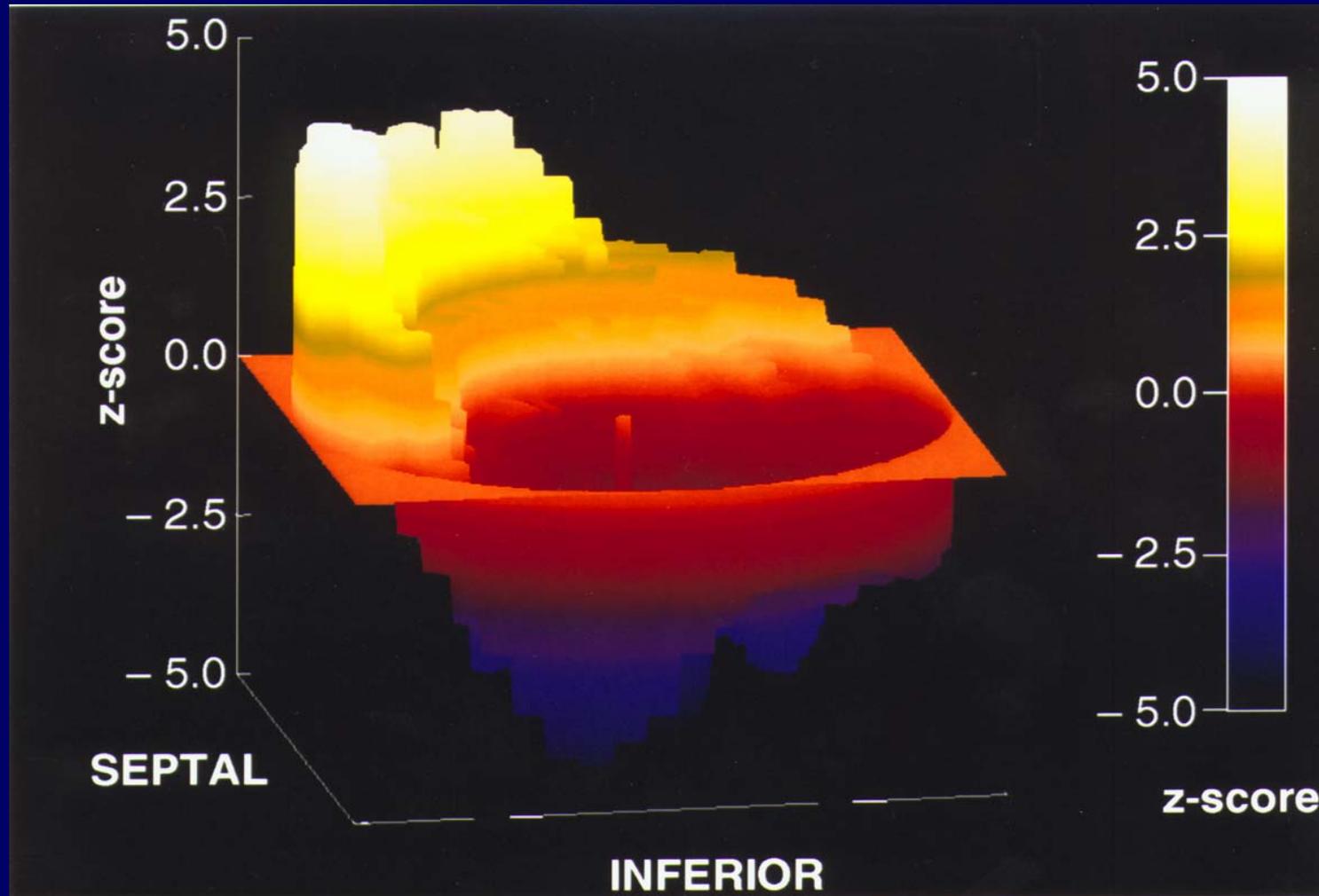
FLOW



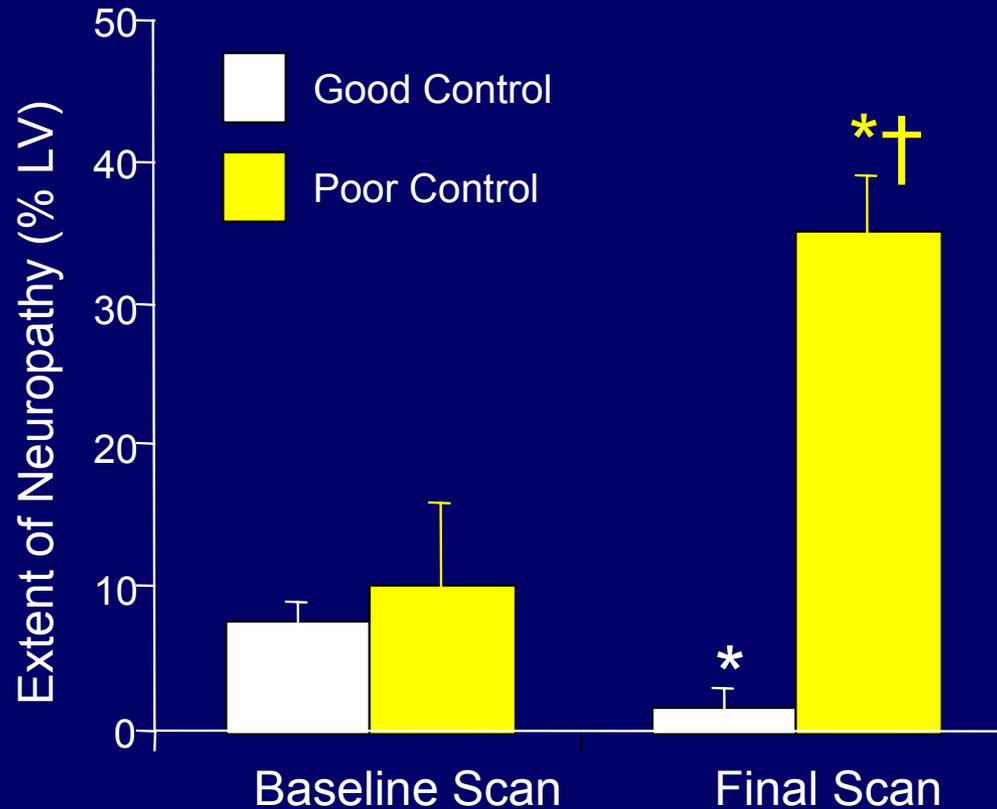
C-11 HED



Increased Sympathetic Nerve Fiber Density in the Proximal Left Ventricle Contrasts with Loss of Distal Nerve Fibers in Cardiovascular Autonomic Neuropathy



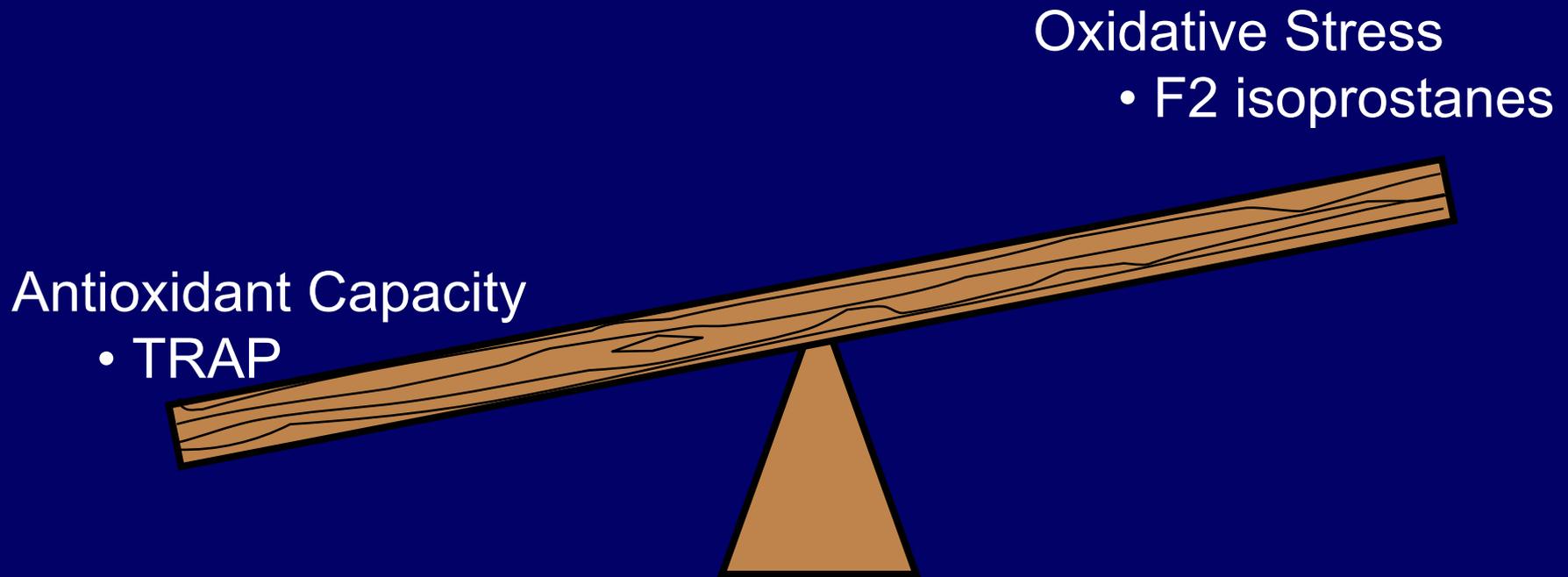
PET-HED Can Detect Progression and Regression of Cardiovascular Autonomic Neuropathy Over 3 Years in Type 1 Diabetes



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- Peripheral neuropathy
- EDIC results: ? Metabolic memory
- Cardiac autonomic neuropathy
- Surrogate markers: urine, sera, skin biopsies
- New NIH initiative: AMDCC

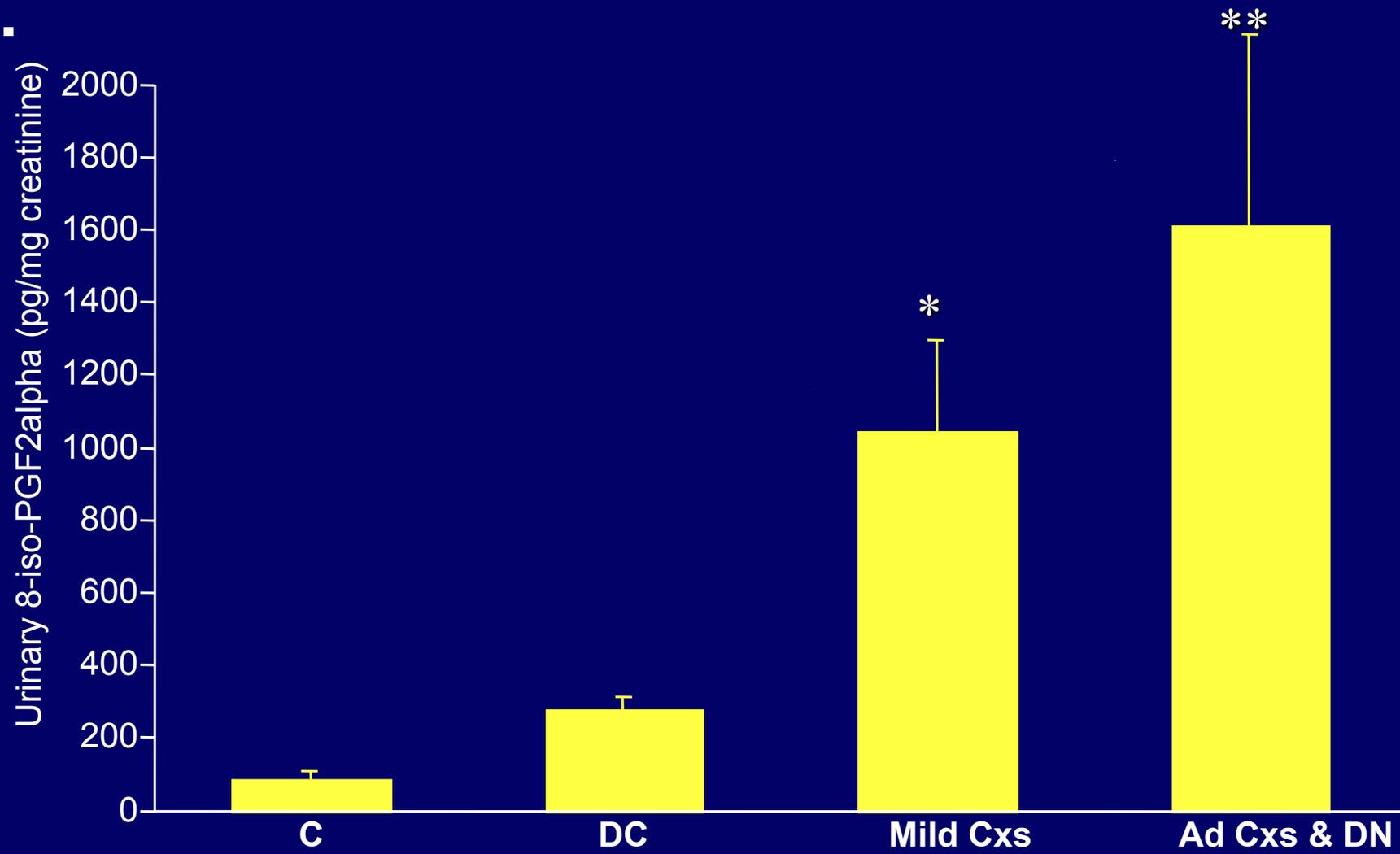
In Diabetic Neuropathy the Balance Favors Oxidative Stress



TRAP = Total Radical Trapping Antioxidant Parameter

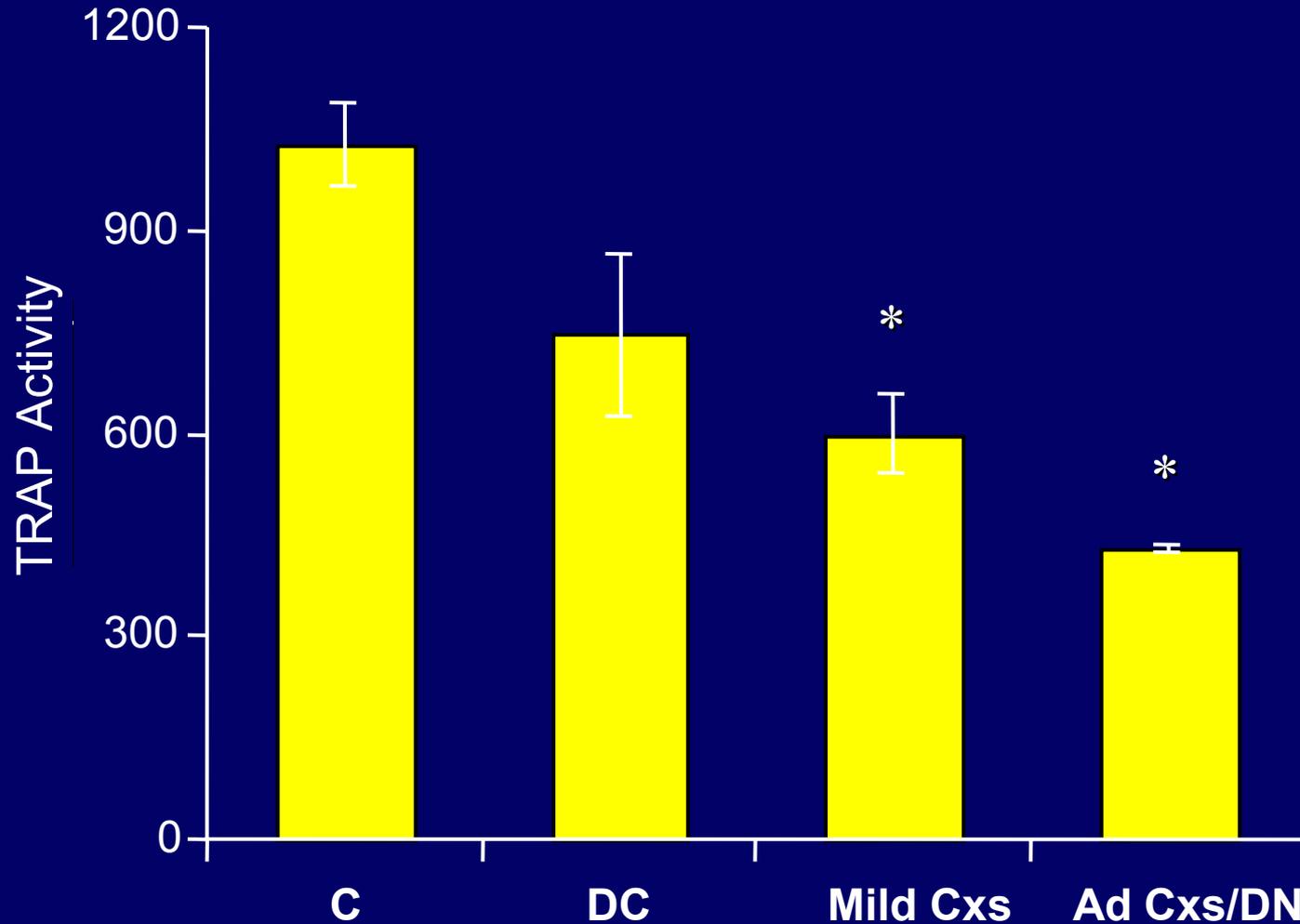
Urine F2-Isoprostanes (a Marker of Systemic Oxidative Stress) are Increased in Diabetic Subjects With Early Complications

a



* $p < 0.05$, ** $p < 0.01$ vs C & DC

TRAP Activity (a Measure of Oxidative Stress Buffering Capacity) is Decreased in Patients With Diabetes and Complications.



*P<0.05 vs. C

The Skin Biopsy Technique I



The Skin Biopsy Technique II



The Skin Biopsy Technique III

HEALED SITE: 2 months



The Skin Biopsy Technique V



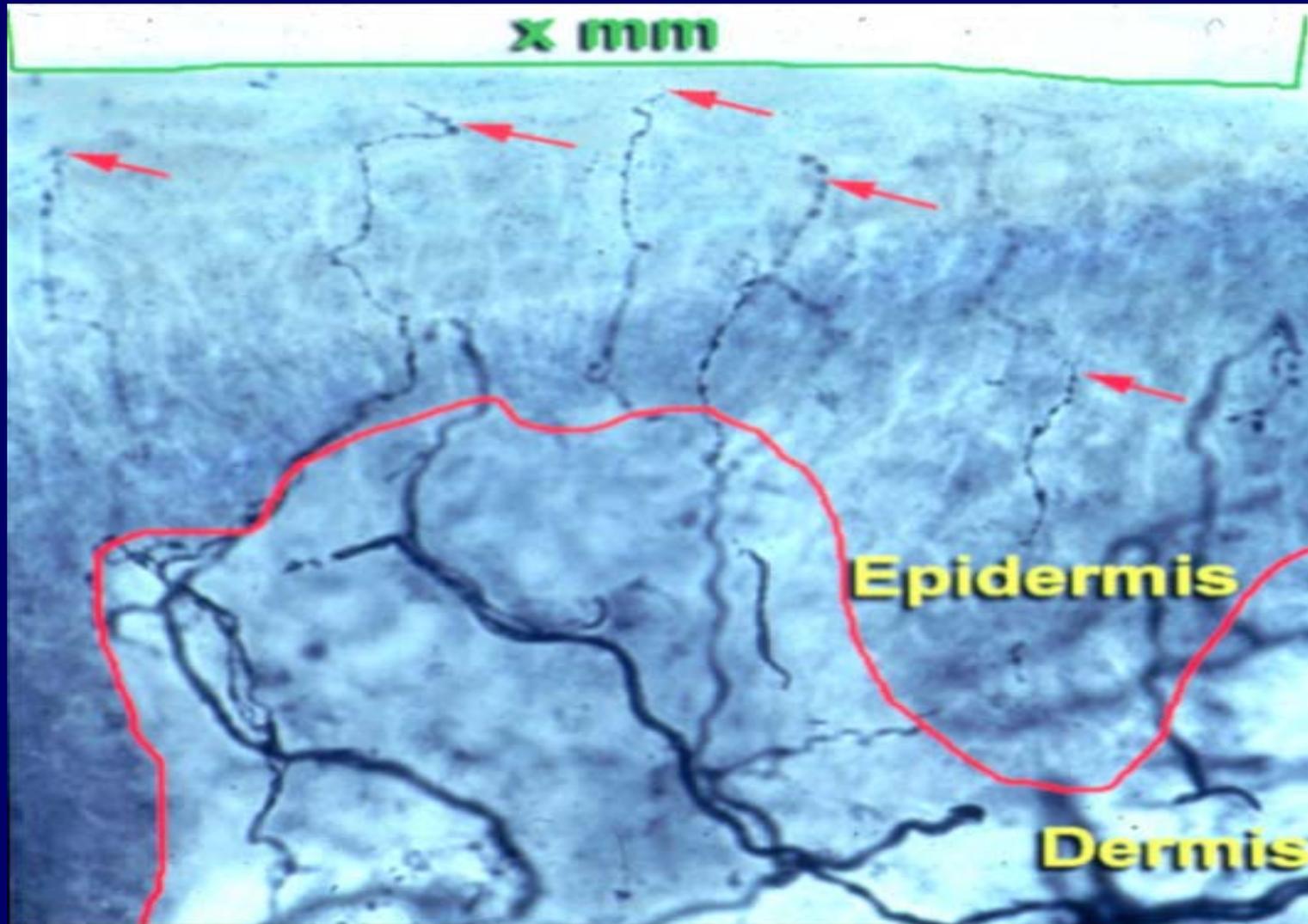
The Skin Biopsy Technique VI



The Skin Biopsy Technique VII

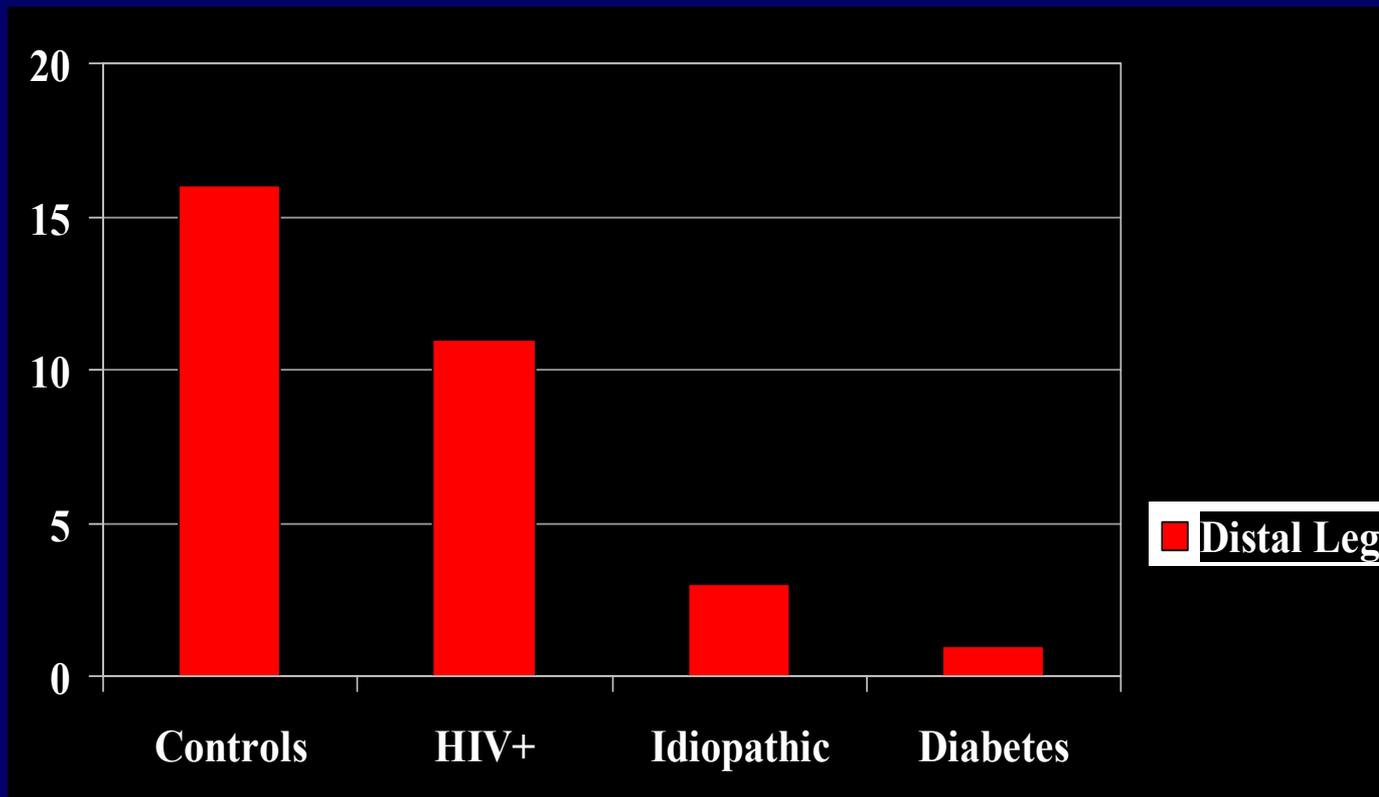


Normal Cutaneous Innervation Assessed with Skin Biopsy



Epidermal Nerve Fiber Densities

Epidermal Nerve Fiber Density

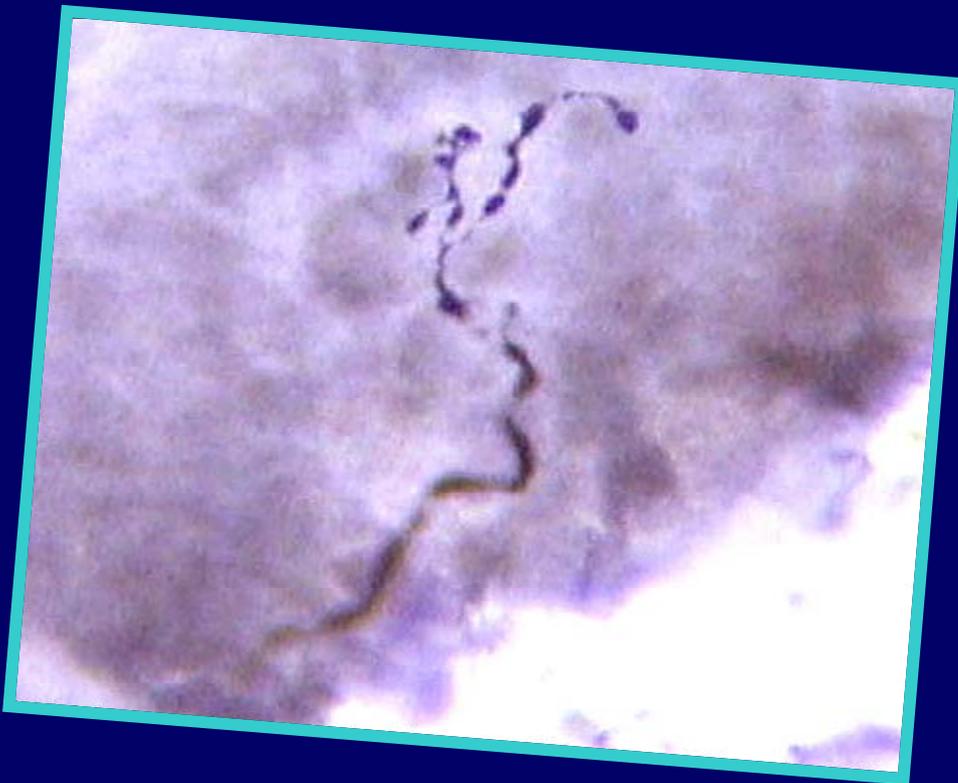


Strategy: Regeneration in EDIC: Correlation with Neurologic and Urologic Status?

- Epidermal nerves are attractive
 - Easily accessible
 - Biopsied in a relatively non invasive procedure
 - Re-biopsied
 - Available 'chemical' insult: capsaicin
 - Can assess regenerative capacity



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UNIVERSITY***

Capsaicin Model

